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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
502-120PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB99/01415	22/07/1999	24/07/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant UNIVERSITY OF OTTAWA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which hav been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/02/2000	20.06.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Chavanne, F Telephone No. +49 89 2399 8399

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB99/01415

I. Basis of the r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-53 as originally filed

Claims, No.:

1-67 with telefax of 28/08/2000

Drawings, sheets:

1/13-13/13 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with r gard to novelty, inventiv step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-49, 51, 52, 57-67
	No:	Claims	50, 53-56
Inventive step (IS)	Yes:	Claims	1-44, 59-67
	No:	Claims	45-58
Industrial applicability (IA)	Yes:	Claims	1-23, 45-61
	No:	Claims	24-44, 62-67

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The examination of the present application has been performed assuming that the claimed priority is valid. However, it is noted that intermediate documents would then become relevant to assess the patentability of any claimed subject-matter not entitled to said priority.

2. Reference is made to the following document:

   D1: WO 98/22131

3. The subject-matter of claim 50 relates to a purified nucleic acid characterised in that it hybridises to a probe comprising at least ten nucleic acids from the XIAP IRES. However, this characterisation corresponds to a result to be achieved and not to technical characteristics, and thus, cannot be considered as an element of novelty for said nucleic acid. Thus, the subject-matter of claim 50 corresponds to a purified nucleic acid. Such a subject-matter is well-known in the art. Thus, claim 50 is not novel.

   The subject-matter of claim 53-56 refers to a nucleic acid comprising a nucleotide sequence complementary to at least 14 nucleotides of a nucleotide sequence comprising downstream of a XIAP IRES a nucleotide region which differs from the corresponding naturally occurring XIAP region (e.g. any sequence encoding a polypeptide differing from the corresponding XIAP). Thus, numerous antisense nucleic acid molecules, catalytic RNAs, etc..., including known ones fall within the scope of these claims. Thus, the subject-matter of claims 53-56 is not novel.

   Therefore, claims 50 and 53-56 do not meet the requirements of Article 33(2) PCT.

4. The subject-matter of claims 45-49, 51 and 52 refers to a nucleic acid comprising a XIAP IRES. Said nucleic acid may also comprise downstream of said XIAP IRES a nucleotide region, which differs from the corresponding naturally occurring XIAP

region in at least one nucleotide.
According to claims 45-47, 51 and 52, the region downstream of the XIAP IRES may differ from only one nucleotide but may also totally differ from the naturally occurring corresponding region. In claims 45-47 it is further specified that the XIAP IRES "increase cap-independant translation of a cistron when located upstream from said cistron within a mRNA molecule" (claims 45 and 47) under stress conditions (claim 46). However, it is the main characteristic of an IRES to allow cap-independant translation of a linked protein-encoding sequence. XIAP is an apoptotic suppressor and is expressed in response to apoptotic stimuli. Thus, it is an implicit feature of the XIAP IRES to "increase cap-independant translation of a cistron when located upstream from said cistron within a mRNA molecule" under stress conditions.
The XIAP IRES corresponds to the 3' extremity of the XIAP promoter region (see page 12, line 26 to page 13, line 7 of the description). Thus, a purified nucleic acid comprising the XIAP promoter linked to a coding sequence other than the XIAP coding sequence would fall within the scope of claims 45-47, 51 and 52.

D1 provides a method for identifying a compound that stimulates or inhibits apoptosis. In said method, a mammalian cell is transfected with a nucleic acid comprising a reporter gene operably linked to a XIAP promoter. D1 mentions the use of the methods it discloses for gene therapy (abstract; page 5, lines 3-15; page 22, line 15 to page 23, line 13).
The subject-matter of claims 45-49, 51 and 52 differs from D1 in that the nucleic acid mentioned in D1 has not been purified. However, nucleic acid construction and purification technics are well-known in the art and routinely applied. Thus, in view of D1, the man skilled in the art would not require any inventive skill to come to the subject-matter of claims 45-49, 51 and 52. As a consequence, said claims are not inventive.
The subject-matter of claim 57 further differs from D1 in the sequence located downstream of the XIAP IRES. However, knowing the anti-apoptotic function of XIAP, the man skilled in the art would not require any inventive skill to come to the subject-matter of claim 57. The use of a tissue-specific promoter to obtain tissue-specific expression of a particular gene product is well-known in the art. Thus, by applying common knowledge, the man skilled in the art would also come to the subject-matter of claim 58. As a consequence, claims 57 and 58 are not inventive.

Therefore, claims 45-49, 51, 52, 57 and 58 do not meet the requirements of Article 33(3) PCT.

VI. Certain documents cited

Certain published documents (Rule 70.10)

1. Nature Cell Biology
   Vol. 1, pp. 190-192, 1999
2. WO 98/35693

VII. Certain defects in the international application

1. Claim 14 has been drafted as being dependant from claim 13. The subject-matter of claim 13 is a method for identifying a compound that decreases XIAP IRES-dependant translation, whereas the subject-matter of claim 14 is a method for identifying a compound useful for treating cancer. Said subject-matters differ from one another, thus claim 14 cannot be dependant from claim 13.

2. Claim 20 has been drafted as being dependant from claim 19. The subject-matter of claim 19 is a method for identifying a compound that modulates protein translation, whereas the subject-matter of claim 20 is a method for identifying a compound for treating cancer. Said subject-matters differ from one another, thus claim 20 cannot be dependant from claim 19.

3. Claims 38, 40 and 42 have been drafted as being dependant from claim 28. The subject-matter of claim 28 is a method for regulating the level of a protein in a cell, whereas the subject-matter of claims 38, 40 and 43 is a method for inhibiting apoptosis in a cell, a method for reducing hypoxic stress in a tissue under hypoxic stress, and a method for stimulating apoptosis in a cell, respectively. Said subject-matters differ from one another, thus claims 38, 40 and 42 cannot be dependant from claim 28.

4. Although claims 47-49, 51 and 52 have been drafted as separate independant

claims, they relate to the same subject-matter: a purified nucleic acid comprising a XIAP-IRES. Thus, it appears appropriate to amend said claims by defining the relevant subject-matter in terms of one single independant claim followed by dependant claims covering the optional features (Rule 6.4 PCT).

5. Claims 66 and 67 are dependant from claim 25. Thus, it appears appropriate to move said dependant claims closer to independant claim 25.

VIII. Certain observations on the international application

1. Claims 45-47, 49, 50 and 53 which refers to a purified nucleic acid molecule attempts to define the subject-matter in terms of a result to be achieved ("increases...", "encoding...", "hybridises..."). Such a definition is only allowable in case the invention can only be defined in such terms. However, this prerequisite is not met by the instant case since a nucleic acid is a chemical compound which has to be characterised by structural features. Therefore, claims 45-47, 49, 50 and 53 do not meet the requirements of Article 6 PCT (see also Guidelines C-III, 4.7 PCT).

2. The subject-matter of claim 24 refers to a method for regulating the level of a protein in a cell. However, it is not clear from the formulation of said claim, how said method has to be pursued. In fact, the mere transformation of a cell with a nucleic acid comprising a XIAP IRES sequence does not regulate a protein. Moreover, it is not clear which protein is concerned by said method. Dependent claims 25, 26 and 28 further refers to a polypeptide. The relation between said polypeptide and the above mentioned protein is not clear (Article 6 PCT).

4. Claims 51-53 lack clarity due to the term "substantially". This term is not suitable to clearly define the scope of the claim, because it is without technical significance and its vagueness makes it entirely opened to individual interpretation. Therefore, claims 51-53 do not meet the requirements of Article 6 PCT.

5. For the assessment of the present claims 24-44 and 62-67 on the question whether they are industrially applicable, no unified criteria exist in the PCT

Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.